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A Review on Electrophysiology based Detection of Diabetic Retinopathy

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Abstract

Complications of diabetes will result in Diabetic Retinopathy. The patient will not be aware of the symptoms unless it's too late to carryout treatment. Thus early detection of diabetic retinopathy is very essential to prevent vision loss. Fundus examination is the major method of diagnosis to detect Microvasculature changes, but a visual functional test is an effective alternative to this method which has potential to detect Diabetic retinopathy in early stages. Components of visual function can be characterized in by electrophysiological test of the of the retina.

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1. Introduction

One of the common complications of diabetes is Diabetic retinopathy (DR). Retinopathy is still a serious cause of vision loss [1-2]. Prevention and early treatment of Diabetic retinopathy is more challenging, since symptoms usually not noticed in the early stages. Diabetic Retinopathy can be of two types, Non-proliferative Diabetic

Retinopathy and Proliferative Diabetic Retinopathy. Early stage of the Diabetic Retinopathy is referred to as Non-proliferative Diabetic Retinopathy. The advanced stage of DR is Proliferative diabetic retinopathy.

The micro vascular changes and retinal neurodegeneration is a component of DR [3]. The previous studies revealed that diabetes increases the rate of apoptosis of cells in the retina, including neurons. Thus, the Diabetic Retinopathy is considered a chronic neurodegenerative disease of the retina.

Fundus examination is the major method of diagnosis through which vascular lesions and macular edema can be visually noticed but, it does not reveals the visual functionality. The Diabetic Retinopathy results in noticeable difference in vision in the early stage[4]. The functional components of vision which are altered in measurable ways are blurred vision, dark areas in vision, reduced night time vision, impaired colour perception. Due to Diabetic Retinopathy the electrophysiological characteristics shown significant defects in retinal response to light.

Visual function can be checked by retinal response to acuity, dark adaptation, contrast sensitivity, and colour contrast. There are data revealing that these functional parameters is varied in people with diabetes. This clearly shows that variation in the vision functionality have not been fully utilized for detection of DR.

2. Visual Functionality Checking Methods

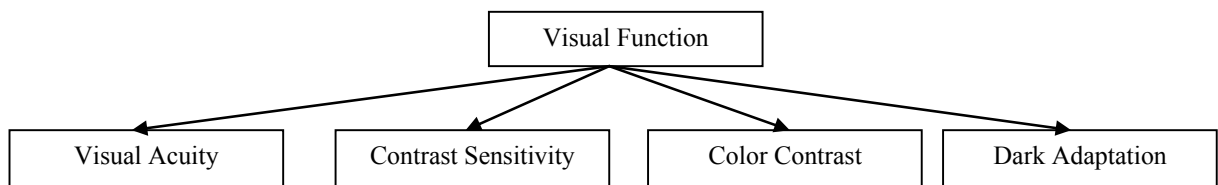


Figure 1. The types of clinical testing methods of Visual Functionality

Figure 1. shows the different clinical testing methods of visual functionality. Each of these methods have a specific role in testing visual functionality. The following section describes all these methods briefly.

Visual function is checked by a non-invasive functionality called Visual acuity. Visual acuity functionality is tested by using a chart which contains rows of letters of decreasing sizes in each row. Scores reflect the ability of a person to identify individual letters of different sizes in the charts, it indicates the retinal spatial resolution. It is observed largely that visual acuity is varied due to diabetic retinopathy and visual angle is doubled with age, period of diabetes, severity of diabetic retinopathy. No major difference was found while comparing the early DR group with non-diabetic normal groups. Therefore, Visual acuity is significantly reduced as DR progresses, but this sensitivity is insufficient to identify the early stages of DR[5].

The retinal ability to uniquely identify different shades of gray is called contrast sensitivity. Several studies have shown reduced contrast sensitivity in diabetic patients[6]. contrast sensitivity test is potentially highly sensitive to retinal function compared to that of Visual acuity. contrast sensitivity is thus considered as a detector of early retinal defects. It is reported that while contrast sensitivity testing revealed differences between healthy subjects and diabetic subjects with early DR, and diabetes with more progressive DR. However, the test did not shown differences between these diabetic sub-groups and therefore may not be able predict the progress of the DR. The sensitivity of contrast sensitivity is carried out by comparing scores of non-macular edema subjects and normal subjects. This comparison reveals that subjects without macular edema had significantly reduced contrast sensitivity scores compared to normal subjects. Unlike Visual acuity testing, contrast sensitivity differences were detected in the absence of obvious signs of DR, suggesting greater sensitivity of this test.

Colour vision, is usually tested with the 100-Hue test, it has been observed that colour vision declines in diabetic people. Previous studies has shown some defects in colour vision. However it did not able to correlate this colour vision decline with respect to the period of diabetes or extremity of Diabetic Retinopathy. The non-proliferative diabetic retinopathy patients have experienced significant deficits in blue-yellow colour contrast. Colour sensitivity is examined by using clinical electrophysiology also. A flash-on-flash protocol was used in a group of diabetic patients but there were no signs of DR, in which a blue spot was paired with a short blue flash on a yellow background to isolate the S-cone pathway. The pre-proliferative DR patients experienced decreased response to S-cone stimulation in comparison with that of age-matched normal subjects. In another approach which used different colours of flash stimuli has resulted in reduction of amplitude of the ERG b-wave of S-cones, in diabetic patients.

but it was unable not correlate this observation with the blood glucose or presence of Diabetic Retinopathy. Thus, it suggests a lack of full dependence on vascular pathology and defects in visual function.

Dark adaptation is the response of the retina when moving from bright light to low illumination conditions. At low levels of light, the rod photoreceptors are active and its response are responsible for vision, while the cones are less active; this is referred to as scotopic vision. Therefore, dark adaptation is nothing but the adjustments made within the retina to result in scotopic vision. Dark adaptation is measured by first subjecting the retina to adapt to darkness for some time. Then the retina is stimulated by a bright flash of light the response of the retina is obtained as an electrical signal through electrodes mounted at the cornea of the eye. The time taken for the retina to return to a specific threshold of sensitivity is measured. In case of early Diabetic Retinopathy it is seen that the response time is significantly extended from that of dark adaptation compared to non-diabetic subjects, Thus it is considered as a good sensitive marker of early Diabetic Retinopathy [7].

By using a dark adaptometer to measure dark adaptation in diabetic subjects ranging from 3 months to 51 years duration, diabetes patients adaptation to scotopic conditions was delayed and also had elevated thresholds showing reduced sensitivity to light.

Due to more energy consumption and neurotransmitter release from photoreceptors, The retina is metabolically very active during the dark than the light. Thus it is evident that Diabetic Retinopathy is exacerbated during dark adaptation since there increased demand for energy of photoreceptors [8,9]. A recent functional MRI study confirmed that a greater metabolic activity is localized to the outer retina in dark-adapted rats, compared to the inner retina [10]. In the dark-adapted retina the differential neural activity is affected by diabetes. Visual function which is an important aspect has been largely neglected by researchers in Diabetic Retinopathy research.

3. Electrophysiology Methods

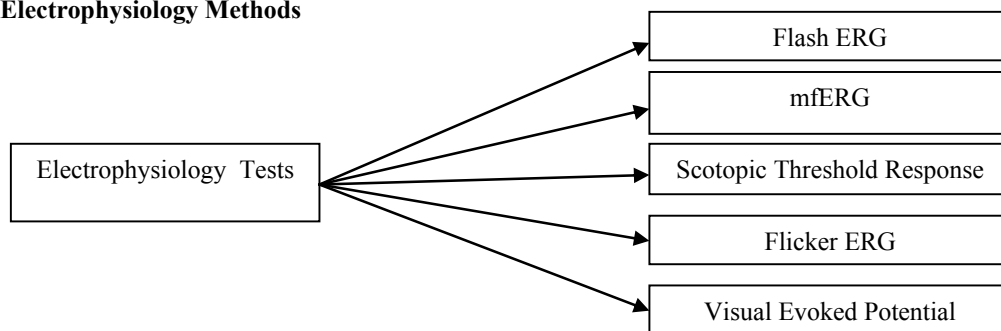


Figure 2. Types of Electrophysiological Tests

Figure 2 Shows the different types of Electrophysiological clinical testing methods. The following section describes all these methods briefly.

When a light flash falls on the retina, a large amount of photoreceptor cells are activated. This process includes changes in the interlayer currents, determining variations in the trans-retinal voltage: its temporal evolution is recorded in the Electroretinogram (ERG). Understanding the specific features (onset, time delay, amplitude, line shape) of the ERG components and their relationship represents the principal aim of past and present research in the field of ocular electrophysiology[11].

In our earlier paper Umashankar, Panse et al discussed an initial work on analysis of ERG to detect CSNB and Achromatopsia abnormalities of the eye. In this paper we discuss a new system to detect Diabetic Retinopathy [12]. The Flash ERG illustrated in Figure -3. Is a response recorded using a recording system with a wide frequency range, and evoked by a bright flash in order to record all components. The ERP is a rapid discharge recorded with an extremely high intensity flash in a well dark – adapted eye using high – frequency amplifiers.

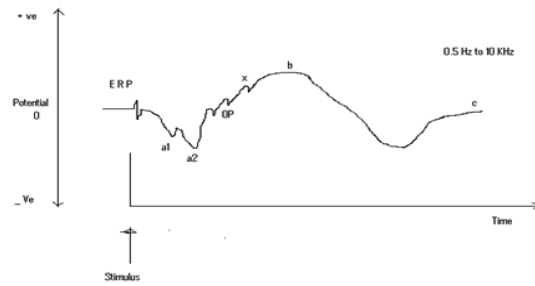


Figure 3. The Electroretinogram (ERG) Signal

Table 1. lists the components of the ERG wave and its origin. The a – wave is a negative potential generated extracellularly at the radial path in the cell body of the photoreceptors which hyperpolarize as a response to light, and is an important parameter of the ERG in measuring of photoreceptor activity. The a – wave consists of two components i.e., a1 and a2, arising from the cones and rods respectively.

Table 1. ERG waveform components

Key	Full name of component		Generator
ERP	Early Receptor Potential		Outer segment of Photoreceptors
a1, a2	a - wave		a1 – cones, a2 - rods
OP	Oscillatory Potentials		Amacrine cells
x	x – wave or b1	b - wave	Cells in the inner nuclear layer
b	b – wave or b2		
c	c - wave		Pigment epithelium

The b – wave is the most readily recordable major component of the clinical ERG. It reflects the postsynaptic summed neuronal activity of the inner nuclear layer and is thus an important measure. B – wave consists of two components, b1 and b2, representing the cone – mediated and rod – mediated responses respectively.

The oscillatory potential (OP) appears as a rapid oscillation on the rising phase of the b – wave of the ERG evoked by a bright flash. The last oscillation is relatively well defined, can be recorded on a open recorder and is called the x – wave or b1. The amacrine cells, the inner plexiform layer and optic nerve fibbers have all been suggested as possible generators of the oscillatory potential.

The c – wave can be seen as a small, slow, positive deflection after the b – wave, although it actually starts slowly from the beginning of light stimulation. Briefly the integrity of the pigment epithelium and photoreceptors is an essential factor for the generation of the c – wave.

The Electroretinogram(ERG) is used time and again as a an approach to detect variation of retinal function due to diabetes. ERG is a good predictor of the progression of DR. ERG measurements have revealed decrease in the amplitude of the b-wave, oscillatory potentials and delay in the implicit times of the ERG waveform in diabetic patients. The Scotopic full-field ERG also shown variation in a-wave, b-wave, and oscillatory potential wave amplitudes and implicit times while analyzing differences between diabetic and NPDR subjects compared to controls [13].

There is good evidence that the amplitude of the scotopic threshold response is reduced in people with diabetes [14-16]. Some reports of ERG recordings also suggest a decrease in the a-wave amplitude and delayed implicit times in diabetic indicating a possible decrease in the magnitude of the photoreceptor response to light [17].

Decrease in the amplitude and implicit times of the oscillatory potentials (OPs) are the most consistent ERG changes

associated with DR. The OPs are wavelets superimposed along the ascending phase of the b-wave, originated from horizontal and amacrine cell activity. The OP's measure is referred to as a predictor of the onset and progression of DR [18-19]. A decrease in both the frequency and amplitude of the OPs, as well as an increase in OPs latency indicates inner retinal malfunctioning.

3.1 The multifocal ERG

Multi-focal ERGs is a technique used to measure the function of localized portions of the retina. An alternating black or white hexagonal pattern from a ultra-high brightness video monitor is used as stimulus for mfERG. The result is displayed as a 3-dimensional ERG response "map" or waveforms from multiple regions of the retina recovered. This test is handy in the differential diagnosis of acuity loss, central serous retinopathy, and age-related maculopathy. [20]. The mfERG consists of three major peaks (PI, N1, and P2), signifying bipolar cell activity. mfERG of diabetic patients shown increase in delay to response revealing malfunction in the localized focal regions of the retina [21-23]. Vascular pathology of DR's electrophysiological response is obtained by mfERG. The increased delay in response implicit times indicates non-proliferative DR. The mfERG is also been used in combination with stereo fundus imaging of non-proliferative retinopathy patients show that areas with abnormal ERG responses were contiguous with areas containing vascular lesions [24-26].

3.2 The scotopic threshold response

In the measure of retinal function the scotopic threshold response (STR) is hardly ever used type of an ERG waveform, Even though it is very sensitive to inner retinal disorders. The patients are subjected to a long period of dark adaptation, thus the measured waveform thereafter is the response to very low intensity flash stimulation. The STR is probably originates from inner retina i.e. retinal ganglion cells and amacrine cells [27]. There is some evidence that the amplitude of the STR is reduced in humans with diabetes. This result was found to also occur in animals. A study by Kohzaki et al., shown that STR amplitudes were altered in diabetic rats to a greater extent than in ERG parameters such as the b-wave amplitude. The discrepancy in the STR of humans and rodents with diabetes hinted an inner retinal dysfunction that most likely involves the ganglion cells. More recently, ganglion cell malfunction was confirmed in diabetic mice and the STR was used to show that retinal ganglion cells can be rescued by pentazocine, a ligand for the sigma receptor. This has shown that the reduced STR amplitude is due to retinal ganglion cell apoptosis, and using a neuroprotective drug can also prevent the reduction in the functional output of inner retina neurons.

The STR is is characterized by two waves: positive STR (pSTR), which possibly reflects ganglion cell activity, and negative STR (nSTR), which comes after the pSTR and possibly reflects amacrine cell activity [24,27]. Kohzaki et al. verified a reduction in the amplitude of the positive component of the STR of dark-adapted diabetic rats, but no difference in the nSTR was observed, signifying that ganglion cell output is modified by diabetes before amacrine cell function is affected. This reduction in pSTR may be because of ganglion cell apoptosis, which is a common consequence of diabetes [28].

3.3 Electrophysiological approaches to study dark adaptation

Electrophysiological approaches when applied to diabetic animals in dark adaptation [29], Tyrberg and colleagues identified a rise flicker response implicit time in dark-adapted diabetic individuals, clearly showing the identifiable delay in dark adaptation [30]. Flicker ERG recorded under low intensity conditions also revealed amplitude reductions in recordings from diabetic rats, indicating reduced retinal sensitivity to light. Paired-flash ERG recording also revealed amplitude reductions, suggesting loss of rod function.

3.4 Visual evoked potentials

The visual evoked potential (VEP) is an electrical signal which is response to a bright flash of light recorded through the skull over the occipital cortex. Changes in the VEP are thought to reflect ganglion cell and optic nerve dysfunction and several clinical studies show deficits in humans with diabetes. While this approach is not often used, several studies have demonstrated that differences in the VEP exist in humans with diabetes. A small clinical

study revealed the presence of functional VEP defects in all diabetic patients, irrespective of the presence of DR [31]. A study on juvenile type 1 diabetic patients revealed that the VEP amplitude was reduced with an increased latency. Then in the absence of vascular retinopathy, the magnitude deficits in VEP increased with longer durations of diabetes [32-34]. These study suggest that damage to optic nerve function occurs in early stages of the disease or can develop independently from the retinal vascular pathology.

4. Proposed Automated Diabetic Retinopathy Detection System

ERG signal of Normal subjects of different age group are collected from hospitals and is simulated. The amplitude, implicit time and spectrum of ERG are obtained and saved for reference. The patient ERG is simulated and compared with the normal ERG parameters. The proposed system first collects the patient's information such as Name, Age from the then it will consider corresponding age groups normal ERG for analysis.

Proposed system consists of Simulation of ERG signal Sub block, Standard ERG and patient's ERG are simulated in this block using ERG data collected from hospitals. The signal conditioning block is meant for noise removal, if the data of the patient is noisy ERG data. The Signal processing, Measurement and Analysis sub block does analysis of the signal using the algorithms developed to obtain the variation in amplitude value and delay in response compared to normal ERG. ERG spectrum of normal and patient are also considered for analysis. After analyzing it will classify the Diabetic Retinopathy in to one of the types as Proliferative Diabetic Retinopathy (PDR)/ Non Proliferic Diabetic Retinopathy depending on the parameter values obtained. The Display of signal and parameters sub block will display all the parameters and obtained from the ERG signal with classification of Diabetic Retinopathy. The Report generation sub block saves the information along with patient's information in to a file for documentation purpose.

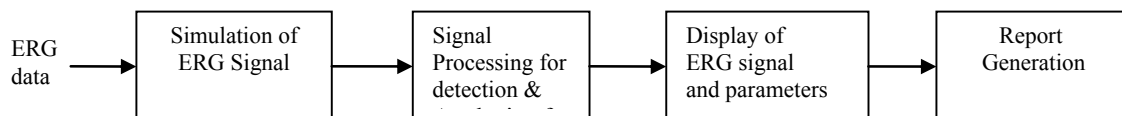


Fig. 2. Block diagram of the proposed automated Diabetic Retinopathy Detecting System

The proposed system will be a low cost alternative to sophisticated costly equipments used in hospitals for the ERG signal analysis purpose. The proposed system can be readily used in hospitals to classify the Diabetic retinopathy accurately since it overcomes observational error or human error during analysis.

5. Conclusion and Future work

Diabetes affects visual function noticeably. Even though there are limitations, it is evident from components of vision, like acuity, dark adaptation, contrast sensitivity, and electrophysiological parameters are differed by diabetes. The different measures of visual function have a strong relation with electrophysiological measures compared to psychophysical one. Electrophysiological measures is an area which requires more attention even today. For instance consider Co-relational studies to compare contrast sensitivity with the ERG, this research area is not been explored. Understanding the causes of disease on visual function is an imperative goal in this field of research. It is evident that electrophysiological approach is largely neglected in the Diabetic Retinopathy field. The accurate measuring and empirically defining of visual function is very difficult. This could be one of the reasons for the gap in research of DR.

The proposed system will be very useful for doctors in electrophysiological analysis for better understanding of the mechanisms and treatments for vision loss in DR. The proposed system will be implemented and tested with Diabetic Retinopathy patient's ERG. The accuracy in classifying Diabetic retinopathy will be obtained. The proposed system will be very useful for doctors to analyze ERG signal since they need not have to analyze ERG signal manually now. Thus it will overcome the possibility of human errors occurrence during observation of the ERG signal.

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